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## Abstract

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The emergence of tolerance to vancomycin (Van) in *S. pneumoniae* in the community is of increasing concern. Recently, a mechanism for the development of tolerance involving the transport-sensor-regulator locus Vex/VncS/R was proposed (Novak et al. *Nature*. 1999;399:590-593). To determine the prevalence of tolerance to Van, 215 strains from the nasopharynx of normal healthy children followed prospectively from birth were tested using kill curves and viability assays. Pulse field gel electrophoresis (PFGE) was used to determine relatedness. DNA sequence of the VncS/R locus in tolerant vs. non-tolerant strains was compared.

Eight (4%) isolates were tolerant to Van: <2 log killing over 4 hours as compared to sensitive reference strain R6. Serotypes of tolerant strains included 3, 6A, 19, 22F, 23, and 29. All 8 tolerant strains expressed the autolysin LytA and were resistant to penicillin. PFGE indicated that the 8 tolerant strains were distinct from each other and that each strain could be paired with a non-tolerant strain isolated from the nasopharynx of the same child at an earlier time. Sequencing data of 8 pairs of strains revealed two alleles each for the death peptide, *pep27*, its transporter, *vex*, and its receptor, *vncS*. In the tolerant isolates, a mismatch of alleles occurred between these three components. This suggests a mismatch might prevent the locus from signaling properly contributing to tolerance in these clinical isolates.

We conclude that Van tolerance has arisen in several different backgrounds and can develop longitudinally during carriage in the same host. Variability in the sequence of the Vex/VncS/R locus is limited and tolerant isolates have a distinct sequence pattern. This may serve as a molecular marker for this emerging antibiotic inhibiting phenotype.



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